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Comparative Utility of Diagnostic Bone-Marrow Components: A 10-Year Study

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Ten years of cumulative experience represented by 4,902 consecutive diagnostic bone-marrow examinations at a tertiary care and referral center were reviewed to assess the value of specific components. While it has been shown previously that the information obtained from each component is generally complementary, the inclusion of some or all components may vary between institutions. The components studied included aspirate smears, clot sections, biopsy cores, and touch imprints of biopsy and clot sections. Three clinical presentations accounted for the majority of cases: staging for carcinoma or lymphoma, cytopenias, and acute leukemia. We conclude that bilateral aspirates with biopsies are required for diagnosis in staging of neoplasms and that a unilateral aspirate with biopsy is sufficient to assess patients with cytopenia or leukemia. Only rarely were touch imprints of biopsy cores necessary to establish a diagnosis; however, their early availability prior to examining sections of the clot and core did provide immediate information, when positive, in the staging of patients with carcinoma. In a small percentage of staging and leukemia cases the diagnosis rested with the clot section alone. The findings in this study address common assumptions associated with routine diagnostic hematology and oncology procedures, and are important to both clinicians and pathologists concerned with accuracy, quality assurance, turnaround time, and cost containment. Am. J. Hematol. 56:37–41, 1997.

Key words: bone marrow; diagnosis; components; utility

INTRODUCTION

It is the generally-accepted standard of practice to evaluate several components in the process of bone-marrow examination, although among different facilities the elements which are specifically included or excluded may vary. At our institution, aspirate particle smears, touch imprints of the aspirate clot and biopsy cores, and paraffin sections of the clot and biopsy are routinely examined in each instance. While such a thorough approach has been advocated by some [1], other emphasize specific components for selected diagnoses [2,3]. We performed a retrospective review of 4,902 consecutive cases evaluated over a 10-year period to determine which components were useful or necessary to establish a diagnosis.

MATERIALS AND METHODS

Four thousand, nine hundred and two bone-marrow procedures were performed between January 1, 1984–December 31, 1993 at the National Naval Medical Center (Bethesda, MD). The procedures were done under local anesthesia using an 8- or 11-gauge Jamshidi like needle (Medical Procedures Inc., Baltimore, MD) after obtaining informed consent. A portion of the aspirate was spread onto glass slides for staining with May-Grünwald-Giemsa and Prussian blue stains, and the remainder was saved for clot section. Touch imprints of the clot and biopsy (both sides if performed bilaterally) were made prior to processing. The core biopsies, which on average each measured 1.5 cm in length, were fixed in 10% formalin, postfixed in B-5, decalcified in 10% aqueous ni-

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TABLE I. Marrow Involvement in Carcinoma

	Total cases	Positive	Bilateral positives	Positive one side only when performed bilaterally (%)
Small-cell lung cancer	501	92	87	26/87 (30)
Breast	97	31	12	7/12 (58)
Nonsmall-cell lung cancer	75	13	11	4/11 (36)
Prostate	34	15	7	1/7 (14)
Other	95	9	4	1/4 (25)
Total	802	160	121	39/121 (32)

TABLE II. Carcinoma Cases Diagnosed Same Day as Procedure

	Positive cases	Aspirate (+)	Asp (−)/ TP (+)	Dx same day (%)
Small-cell lung cancer	92	69	13	82/92 (89)
Breast	31	16	5	21/31 (68)
Nonsmall-cell lung cancer	13	10	2	12/13 (92)
Prostate	15	7	6	13/15 (87)
Other	9	6	2	8/9 (89)
Total	160	108	28	136/160 (85)

Asp = aspirate, TP = touch preparation, DX = diagnosis

tric acid, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Additional special, cytochemical, and immunohistochemical stains on aspirate or biopsy material were performed as indicated. Although aspirate material was occasionally submitted for special studies such as tissue culture, cytogenetics, or flow cytometry, these results were not considered in this study. The aspirate and biopsy touch imprints were examined on the first day of the procedure and a diagnosis was rendered, if possible, to expedite patient care. The clot section, biopsy core, and iron stain of the aspirate and clot section were examined on day 2.

RESULTS

The total number of cases reviewed was 4,902, including 4,235 HIV (−) adults, 160 HIV (+) adults, and 512 pediatric patients. Of the HIV (−) adults, 3,118 (74%) accounted for three presentations: staging for carcinoma or lymphoma, posttreatment follow-up for acute leukemia, and cytopenia. The remaining 1,117 (26%) cases were a heterogeneous group, including 739 evaluated for clinically suspected myelodysplasia, acute or chronic leukemia, myeloproliferative disease, or immunoproliferative disease, and 378 for follow-up of such disorders (excluding acute leukemia). The pediatric cases were excluded from this review, since biopsies in addition to aspirate were not consistently performed.

Among 802 cases evaluated for staging of carcinoma (Table I), 501 were for primary small-cell carcinoma of the lung, 97 for breast carcinoma, 75 for nonsmall-cell carcinoma of the lung, 34 for prostate carcinomas, and 95 for other metastatic neoplasms. Marrow involvement was present in 160 cases; of these, 121 were performed bilaterally, one third of which were positive on one side only (39/121). On the day of the procedure, 136 positive cases were diagnosed on the aspirate alone or by aspirate and touch preparation combined (Table II). Thirty-six cases were ultimately diagnosed on only one component alone: 12 on the aspirate, 2 on the clot section, and 22 on the biopsy.

Eight hundred ninety-four cases represented marrow procurement for staging of lymphoma (Table III). These included 463 for non-Hodgkin's lymphoma, 230 for Hodgkin's disease, and 201 for mycosis fungoides. In nearly all cases of non-Hodgkin's lymphoma the clinical stage was incompletely established or, as in all Hodgkin's disease cases, the presence of disseminated disease was unknown at the time of bone-marrow examination. Among the non-Hodgkin's lymphomas, 129 proved to be low-grade, 192 intermediate grade, and 93 high-grade; in 49 cases adequate data were unavailable to determine grade. Of the 201 cases positive for marrow involvement by lymphoma of any type, 151 were performed bilaterally. Among those performed bilaterally, 35 (23%) were positive on one side only. Eighty-seven cases were considered positive or suspicious on the aspirate and/or touch preparation (Table IV); more than half of the positive cases (105/201) had involvement on the biopsy alone.

Six hundred and one cases with known acute leukemia were reviewed, including 392 with acute myelogenous leukemia (AML), 184 with acute lymphocytic leukemia (ALL), and 25 with mixed phenotype leukemia (Table V). A total of 215 cases showed active marrow involvement. A remission pattern was observed in the remaining patients. The aspirate was diagnostic in 189 cases. Two cases were positive on the clot section alone, and 20 were positive on the biopsy alone.

Eight hundred and twenty-one cases for evaluation of cytopenias were reviewed (Table VI) and included 533 cases for monocytopenia, 198 for bicytopenia, and 90 for pancytopenia. In this group no prior clinical history of lymphoma, myeloproliferative disease, immunoproliferative disease, or carcinoma existed; no peripheral smear features of myelodysplasia, lymphocytosis, or blasts were present. Aspirate alone was diagnostic in 756 cases. The remaining 65 cases required biopsy evaluation in order to diagnose aplasia, multiple lymphoid aggregates suspicious for lymphoma, and granulomas. Monocytopenia accounted for 32 of the cases needing biopsy evaluation for diagnosis, along with 22 cases with bicytopenia, and 11 with pancytopenia. Touch preparations and clot sections were noncontributory in this group.

TABLE III. Marrow Involvement in Lymphomas

	Total cases	Positive	Bilateral positives	Positive one side only when performed bilaterally (%)
NHL, low-grade	129	78	57	16/57 (28)
NHL, intermediate grade	192	58	52	8/52 (15)
NHL, high-grade	93	20	14	3/14 (21)
Hodgkin's disease	230	15	12	5/12 (42)
Mycosis fungoides	201	30	16	3/16 (19)
Total	894[a]	201	151	35/151 (23)

[a]Sum includes NHL cases of unknown grade.
NHL = non-Hodgkin's lymphoma

TABLE IV. Lymphoma Cases Diagnosed Same Day as Procedure

	Positive cases	Aspirate (+)	Asp (−)/ TP (+)	Dx same day (%)
NHL, low-grade	78	27	1	28/78 (36)
NHL, intermediate grade	58	25	6	31/58 (53)
NHL, high-grade	20	10	2	12/20 (60)
Hodgkin's disease	15	0	0	0/15 (0)
Mycosis fungoides	30	15	1	16/30 (53)
Total	201	77	10	87/201 (43)

NHL = non-Hodgkin's lymphoma
Asp = aspirate, TP = touch preparation, Dx = diagnosis

TABLE V. Follow-Up of Leukemia

	Cases	Positive cases	Aspirate (+)	Asp (−)/ TP (+)	Dx same day (%)
AML	392	139	121	2	123/139 (88)
ALL	184	64	56	2	58/64 (91)
Mixed	25	12	12	0	12/12 (100)
Total	601	215	189	4	193/215 (90)

Asp = aspirate, TP = touch preparation, Dx = diagnosis

TABLE VI. Cases Presenting as Cytopenia

	Cases	Aspirate positive (%)	Biopsy needed (%)
Anemia	365	344 (94)	21/365 (6)
Leukopenia	60	56 (93)	4/60 (7)
Thrombocytopenia	108	101 (94)	7/108 (6)
Bicytopenia	198	176 (89)	22/198 (11)
Pancytopenia	90	79 (88)	11/90 (12)
Total	821	756 (92)	65/821 (8)

DISCUSSION

While it has been shown previously that the information obtained from each component of the bone-marrow examination is generally complementary [1], standard inclusion of all components varies widely between institutions. This may be due in part to recommendations based on small sample size and/or selected diagnoses [2,3]. The significance of this variation is unknown but could conceivably alter diagnostic accuracy, efficiency, and turnaround time. We reviewed 4,902 bone marrows representing 10 years of cumulative experience at a tertiary referral center in order to compare the results of this very large group with procurement standards in the literature concerning the usefulness of aspirate, core biopsy, clot section, and touch preparations. In this series, two thirds of patients undergoing bone-marrow examination presented for staging of malignancy (carcinoma or lymphoma), intratherapeutic follow-up for acute leukemia, or evaluation of cytopenia.

In the past, various recommendations have been made for bone-marrow staging of carcinomas and lymphomas. For staging of carcinoma, biopsy alone or biopsy plus aspirate has been suggested [2], with positivity on aspirate alone found between 30–50% [4]. One recent study suggests that aspiration alone is sufficient to diagnose metastatic small-cell lung carcinoma [5]. We conclude that evaluation of bone-marrow aspirate and companion core biopsy is necessary for complete evaluation in the staging of carcinoma, since 25% of small-cell lung carcinomas and 32% of carcinoma cases overall in our series would have been missed on aspirate alone. Similarly, in previously reported series of lymphoma, between 69–82% were diagnosed on the aspirate alone [4,6]. This has also been our experience in intermediate and high-grade lymphomas and mycosis fungoides. However, in low-grade lymphoma cases, only 36% were positive on the aspirate or touch imprint; biopsy was essential in the remainder. In Hodgkin's disease, 6% of cases for staging showed bone-marrow involvement; none were known to have disseminated disease prior to marrow examination and were thus upgraded to Ann Arbor stage IV. In addition, all cases with such marrow involvement were detected on the biopsy alone. Although marrow involvement with Hodgkin's disease is infrequent, the inclusion of bone-marrow biopsy has a significant impact on subsequent treatment and outcome in patients where higher-stage disease has not yet been diagnosed or has been missed by other means.

We also recommend that biopsies performed for carcinoma and lymphoma staging should be done bilaterally. Bilateral evaluation is justified, since 32% of our carcinoma cases and 23% of lymphomas were positive on one side only. Assuming that half of the patients with marrow disease when sampled on one side alone would prove negative by chance, it follows that the lesion would be missed in 11–16% of patients on unilateral biopsy. These findings concur with previous reports; in one study, 27% of 71 total cases of non-Hodgkin's lymphoma, Hodgkin's disease, and metastatic carcinoma were positive on one side only when performed bilater-

ally [7], while in another report 30% of 99 cases of non-Hodgkin's lymphoma were positive unilaterally [8]. The relative ease of performing an additional biopsy, as well as the potential savings in time and expense over other staging procedures, renders the effort justifiable.

Although we observed that aspirates and touch preparations were not entirely complementary in positive cases, their earlier availability allowed confirmation of bone-marrow involvement 1 day sooner in 85% of carcinomas. The importance of obtaining an aspirate is further supported in that 9% of cases which were positive for metastatic disease were observed in the aspirate alone. We also found that the inclusion of touch imprints increased the positive yield in carcinoma cases over aspirate alone by 17%, although our data do not allow us to draw any conclusions concerning clot section vs. biopsy core. In contrast to previous reports concerning lymphoma [4,6], aspirates and touch preparations were diagnostic in less than half (43%) of our cases, highlighting the limited utility of these components without a complementary biopsy. The latter allowed detection of lymphoid aggregates, and their number and location, as well as serving as a source for immunohistochemistry, features previously recognized in definitive diagnosis [8,9–11]. No gain in turnaround time was afforded by the aspirate or touch preparations such as was seen in carcinoma staging, and only 2 cases of lymphoma were diagnosed on the aspirate alone. Finally, we recognize the utility of the clot section, since 1–2% of all the carcinoma and lymphoma cases we reviewed were detected only in this component.

Other observers have recommended unilateral biopsy and aspirate as adequate for evaluation following treatment of AML to estimate cellularity, stage of marrow reconstitution, and detection of early relapse [12–14]. These parameters are less established for ALL, and current protocols allow for the management of residual disease based on aspirate findings only. We recommend unilateral aspirate and biopsy to monitor therapy in AML and ALL. In our review, 10% of AML and ALL cases were positive on the biopsy but not the aspirate; however, we do not suggest that biopsy should replace the aspirate, since 12% of AML and 8% of ALL cases were positive on the aspirate alone. Touch preparations did not significantly improve diagnostic accuracy or turnaround times. Similar to our experience in carcinoma and lymphoma cases, 1% of the leukemias were diagnosed on the clot section alone.

There is a relative paucity of information in the literature specifically addressing or comparing the components of bone-marrow examination in the evaluation of cytopenias. Standard texts recommend performing a biopsy in addition to an aspirate for evaluation of bicytopenias and pancytopenias [15]. We agree with this approach, since 11% of bicytopenia cases and 12% of pancytopenia cases in our series (generally divided between aplasia, evolving lymphoproliferative disorders, and granulomas) were diagnosed solely on the biopsy. In contrast, the aspirate alone has usually been considered sufficient for monocytopenias [15]. We feel that inclusion of the biopsy is warranted in all monocytopenia presentations as well, since 6% of our monocytopenia cases required biopsy for diagnosis. An additional 8% of cytopenia cases were diagnosed with myelodysplastic syndrome, immunoproliferative disorder or carcinoma, leukemia, or myeloproliferative disease. Although in these instances we found that biopsy was not necessary for diagnosis, the role of biopsy in each of these conditions has been previously established [3,16–18]. Our findings complement these studies and further highlight the potential value of the biopsy in evaluating cytopenias.

In summary, we reviewed 4,902 consecutive bone-marrow examinations performed over a 10-year period at a tertiary care facility to determine the usefulness of various components. We conclude that bilateral biopsies are necessary to stage carcinoma and lymphoma. Aspirates and touch preparations hasten the diagnosis in a significant number of carcinoma cases. Unilateral aspirate and biopsy are considered appropriate for follow-up of acute leukemia and for evaluation of cytopenias. The clot section retains its importance as the only diagnostic preparation in a small number of cases, as well as its corroborative usefulness in many instances.

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